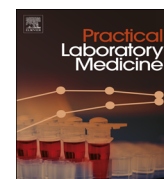


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The stability of quantitative blood count parameters using the ADVIA 2120i hematology analyzer

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ABSTRACT

Objectives: To evaluate the stability of complete blood count (CBC) parameters by measuring at multiple time points up to 72 h after venepuncture.

Methods: 36 samples submitted for routine haematology were measured at 0, 8, 24, 48, 72 h. 18 samples were kept at room temperature (23–25 °C) and the other 18 at 4 °C. The stability of the CBC parameters was determined by comparing the results to the 0 h sample. White Blood Cell Count (WBC), Hemoglobin (Hb) concentration, Red Blood Cell (RBC) count, Hematocrit (Hct), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Cellular Hemoglobin Concentration Mean (CHCM), Mean Platelet Volume (MPV), RBC distribution width (RDW), Platelet (PLT) and Reticulocyte counts were studied.

Results: Most parameters were stable for 24 h at 4 °C, except for MCV, MCHC, CHCM and MPV. MCV and MPV increased after 8 h ($p < 0.0001$), whereas MCHC and CHCM decreased significantly after 8 h. Significant changes were found for MCHC in samples kept at 4 °C for 48 h ($p = 0.002$), and for CHCM kept for 72 h ($p < 0.001$). Reticulocyte count stability was maintained for 24 h at 4 °C ($p = 0.3047$). In samples kept at room temperature changes occurred after 8 h in RBC, Hct, MCV, MCH, MCHC, CHCM, MPV and PLT.

Conclusion: CBC measurements are reliable for 8 h when samples are stored at room temperature. The only parameter stable for 72 h at room temperature was Hb. Blood samples kept at 4 °C for up to 24 h are suitable for haematological analysis.

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1. Introduction

Sample stability, a factor of the pre-analytical phase, is an important component of clinical laboratory results. Published values for total testing error range widely from 0.1% to 9.3%, and this broad range includes both pre- and post-analytical errors. Moreover, studies of factors within the pre-analytical phase including specimen collection, handling and storage indicate that 93% of errors are not related to the highly standardized analytical process [1]. Routine hematology results influence both diagnosis and therapy, and it is not uncommon for transport of blood samples to the laboratory to cause up to a day's delay before analysis. Delayed sample analysis could result in changes of measured parameters, complicating the interpretation of results. Instrument manufacturers normally provide data on suitable storage conditions and times, but

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Table 1

Mean and 95% confidence interval (CI) for the mean changes observed in CBC on storage of blood specimens at room temperature and in refrigerator at 4 °C. Hb and Reticulocyte count were not normally distributed at room temperature (see Table 2) , *p* refers to mean differences between the observation at time *t* and the baseline (time 0).

Hours	Room temperature (23–25 °C)					Refrigerator (4 °C)				
	0 Mean 95% CI	8 Mean 95% CI <i>p</i>	24 Mean 95% CI <i>p</i>	48 Mean 95% CI <i>p</i>	72 Mean 95% CI <i>p</i>	0 Mean 95% CI <i>p</i>	8 Mean 95% CI <i>p</i>	24 Mean 95% CI <i>p</i>	48 Mean 95% CI <i>p</i>	72 Mean 95% CI <i>p</i>
WBC (G/l)	7.9 6.79; 9.00	7.9 6.8; 9.01 <i>p</i> =0.93	7.65 6.55; 8.75 <i>p</i> =0.0003	7.37 6.32; 8.42 <i>p</i> <0.0001	7.25 6.22; 8.28 <i>p</i> <0.0001	7.72 6.52; 8.9	7.87 6.72; 9.02 <i>p</i> =0.0564	7.72 6.56; 8.88 <i>p</i> =0.9808	7.60 6.49; 8.72 <i>p</i> =0.2134	7.36 6.26; 8.46 <i>p</i> =0.0340
RBC (T/l)	4.72 4.51; 4.93	4.81 4.59; 5.02 <i>p</i> <0.0001	4.82 4.61; 5.03 <i>p</i> <0.0001	4.83 4.62; 5.04 <i>p</i> <0.0001	4.81 4.6; 5.02 <i>p</i> <0.0001	4.68 4.46; 4.90	4.73 4.5; 4.95 <i>p</i> =0.0086	4.76 4.54; 4.97 <i>p</i> <0.0001	4.76 4.55; 4.98 <i>p</i> <0.0001	4.75 4.53; 4.98 <i>p</i> <0.0001
Hct (l/l)	0.42 0.4; 0.45	0.44 0.42; 0.46 <i>p</i> <0.0001	0.47 0.44; 0.49 <i>p</i> <0.0001	0.48 0.46; 0.51 <i>p</i> <0.0001	0.48 0.46; 0.51 <i>p</i> <0.0001	0.419 0.4; 0.43	0.42 0.40; 0.44 <i>p</i> =0.4123	0.429 0.40; 0.44 <i>p</i> <0.0001	0.42 0.408; 0.446 <i>p</i> <0.0001	0.43 0.41–0.45 <i>p</i> <0.0001
MCV (fl)	91 87.7; 94.26	95.52 89.3; 95.7 <i>p</i> <0.0001	98.19 94.9; 101.48 <i>p</i> <0.0001	101.41 97.67; 105.15 <i>p</i> <0.0001	101.63 97.76; 105.5 <i>p</i> <0.0001	89.8 86.8; 92.79	89.047 86.13; 91.64 <i>p</i> <0.0001	90.2 87.23; 93.16 <i>p</i> =0.0072	89.72 86.8; 92.62 <i>p</i> =0.6021	90.98 88.05; 93.91 <i>p</i> <0.0001
MCH (pg)	30.05 29.4; 31.06	29.53 28.51; 30.54 <i>p</i> <0.0001	29.46 28.4; 30.4 <i>p</i> <0.0001	29.39 28.39; 30.39 <i>p</i> <0.0001	29.53 28.53; 30.54 <i>p</i> <0.0001	29.53 28.57; 30.49	29.36 28.4; 30.3 <i>p</i> =0.1124	29.1 28.2; 29.9 <i>p</i> =0.0001	29.02 28.11; 29.92 <i>p</i> <0.0001	29.27 28.4; 30.14 <i>p</i> =0.0184
MCHC (g/l)	330.38 327.82; 332.95	319.33 317.44; 321.21 <i>p</i> <0.0001	300.05 297.15; 302.95 <i>p</i> <0.0001	290.05 286.93; 293.17 <i>p</i> <0.0001	290.77 287.63; 293.9 <i>p</i> <0.0001	328.73 325.23; 332.23	329.66 325.88; 333.44 <i>p</i> =0.4130	322.73 319.9; 325.4 <i>p</i> <0.0001	323.4 320.7; 326.02 <i>p</i> =0.0002	311.6 318.8; 324.3 <i>p</i> <0.0001
CHCM (g/l)	326.77 322.19; 331.36	316 312.01; 319.98 <i>p</i> <0.0001	288.27 284.31; 292.2 <i>p</i> <0.0001	274.66 270.33; 278.99 <i>p</i> <0.0001	272.11 267.64; 276.57 <i>p</i> <0.0001	326.8 322.63; 330.96	328.86 324.57; 332.62 <i>p</i> <0.0001	325.06 321.03; 329.1 <i>p</i> <0.0001	323.93 319.57; 328.29 <i>p</i> =0.0001	318.86 314.2; 323.82 <i>p</i> <0.0001
RDW (%)	14.78 14.4; 15.17	14.81 14.4; 15.21 <i>p</i> =0.3863	15.02 14.67; 15.36 <i>p</i> =0.0003	15.01 14.65; 15.37 <i>p</i> =0.0009	14.97 14.63; 15.31 <i>p</i> =0.0064	14.72 14.28; 15.17	14.56 14.12; 14.99 <i>p</i> =0.0001	14.66 14.25; 15.07 <i>p</i> =0.0951	14.50 14.08; 14.92 <i>p</i> <0.0001	14.52 14.11; 119.94 <i>p</i> <0.0001
PLT (G/l)	257.38 222.04; 292.73	240.05 208.68; 271.42 <i>p</i> <0.0001	227.94 196.3; 259.58 <i>p</i> <0.0001	217.55 188.03; 247.07 <i>p</i> <0.0001	211.4 182.17; 240.71 <i>p</i> <0.0001	271.73 235.6; 307.85	272.80 236.4; 309.19 <i>p</i> =0.7818	280.26 241.16; 319.36 <i>p</i> =0.0749	284.73 242.5; 326.91 <i>p</i> =0.0195	284.7 242.54; 386.9 <i>p</i> =0.0195

Table 1 (continued)

Hours	Room temperature (23–25 °C)					Refrigerator (4 °C)				
	0 Mean 95% CI	8 Mean 95% CI <i>p</i>	24 Mean 95% CI <i>p</i>	48 Mean 95% CI <i>p</i>	72 Mean 95% CI <i>p</i>	0 Mean 95% CI <i>p</i>	8 Mean 95% CI <i>p</i>	24 Mean 95% CI <i>p</i>	48 Mean 95% CI <i>p</i>	72 Mean 95% CI <i>p</i>
MPV (fl)	7.68 7.42; 7.93	9.22 8.88; 9.55 <i>p</i> < 0.0001	9.85 9.5; 10.19 <i>p</i> < 0.0001	10.3 9.94; 10.67 <i>p</i> < 0.0001	10.3 9.98; 10.61 <i>p</i> < 0.0001	7.51 7.18; 7.84	7.82 7.47; 8.18 <i>p</i> = 0.0055	8.56 8.17; 8.96 <i>p</i> < 0.0001	9.3 9.0; 9.74 <i>p</i> < 0.0001	9.98 9.57; 10.4 <i>p</i> < 0.0001
Hb (g/l)	–	–	–	–	–	137.86 132.44; 143.21	138.46 133.1; 143.8 <i>p</i> = 0.1442	138.46 132.88; 144.04 <i>p</i> = 0.1077	138.13 132.69; 143.5 <i>p</i> = 0.4332	138.93 133.35; 144.5 <i>p</i> = 0.1750
Reticulocyte count (%)	–	–	–	–	–	1.91 ± 0.48 1.64; 2.18	– – –	1.86 ± 0.39 1.64; 2.08 <i>p</i> = 0.3047	1.75 ± 0.40 1.53; 1.98 <i>p</i> = 0.0032	1.66 ± 0.47 1.40; 1.92 <i>p</i> = 0.0006

these data can vary significantly. It has been claimed that blood samples kept either at room temperature (15–25 °C) or at 4 °C for up to 24–48 h generally yield reliable results for complete blood cell count (CBC) and for automated differential leukocyte count [2,3]. White blood cell count has been said to be stable at 4 °C for at least 56 h [4] and some authors have shown sample stability even after one week of incubation at room temperature [5]. Standards for specimen collection, storage and handling have been published by the International Council for Standardization in Hematology (ICSH): the recommended maximum storage intervals for CBC and differential counts were 6 h at 18–22 °C and 24 h at 2–6 °C [6,7]. Because of the lack of consistent data, it was necessary for our laboratory quality assurance to validate the shelf life of samples. Following the ICSH conclusion that there is no change within the first 6 h at room temperature, we performed a stability study from 8 to 72 h at room temperature (23–25 °C) and at 4 °C for CBC measurements on the ADVIA 120 Hematology System.

The 12 CBC parameters studied were: White Blood Cell Count (WBC), Hemoglobin (Hb) concentration, Red Blood Cell (RBC) count, Hematocrit (Hct), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Cellular Hemoglobin Concentration Mean (CHCM), Mean Platelet Volume (MPV), RBC distribution width (RDW), Platelet (PLT) and Reticulocyte Counts.

2. Method and materials

Thirty six randomly selected blood samples collected by venepuncture and anticoagulated with dipotassium ethylenediamine tetra-acetic acid (EDTA) were measured within 1 h of collection on a Siemens ADVIA 2120i hematology analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany). This sample was taken as the baseline (0 h) sample, and further measurements were made at 8, 24, 48, 72 h following the baseline measurement. The samples were taken from out-patients in the morning on an empty stomach as part of routine laboratory testing. Eighteen samples (12 females, 6 males; age range 27–89 years) were kept at room temperature (23–25 °C) and another eighteen samples (13 females, 5 males; aged 24–75 years) were stored at 4 °C. Samples stored in the refrigerator were allowed to equilibrate at room temperature (23–25 °C) before the measurement, according to the manufacturer's instructions [4]. The effect of storage on CBC parameters was determined by comparing the results at 8,24,48 and 72 h to the 0 h (baseline) sample.

3. Statistical analysis

The differences between samples at various time points were evaluated by the paired *t*-test after verification of normal distribution by the D'Agostino–Pearson test. Wilcoxon's test was used for the parameters with non-normal distribution patterns. If the calculated *p*-value was less than 0.05, the mean difference between the paired observations was considered significant. Mean bias and 95% confidence interval for the bias were evaluated using Bland–Altman plots. The percentage variations from the baseline values were compared with standards for desirable bias derived from the intra-individual and inter-individual variability by Ricos et al. [9,10]. The software version used in the study was Med Calc[®] version 15.2.

4. Results

The changes over time in the mean values of normally distributed CBC parameters are summarized in Table 1, and the non-normally distributed parameters (Hb and reticulocyte count at room temperature) in Table 2.

Significant changes were observed after 8 h storage at room temperature in RBC, Hct, MCH, MCHC, CHCM, PLT and MPV. No significant change was found after 8 h storage period in WBC and RDW values. Reticulocyte counts were relatively

Table 2

Data for non-normally distributed parameters at room temperature (23–25 °C). IQR=interquartile range; 95% CI=confidence interval for the median.

Hours	0	8	24	48	72
parameters	Median IQR CI 95%	Median IQR CI 95%	Median IQR CI 95%	Median IQR CI 95%	Median IQR CI 95%
Hb (g/l)	142.5 138; 151 138.39; 149.41	144 139; 151 139; 150 <i>p</i> =0.3258	143.5 138; 150 138.39; 149.6 <i>p</i> =0.25	143.5 138; 150 139.39; 150 <i>p</i> =0.4316	144 139; 151 139; 150.2 <i>p</i> =0.2754
Reticulocyte count (%)	1.85 1.49; 2.43 1.49; 2.42	– – –	0.92 0.8; 1.31 0.8; 1.3 <i>p</i> =0.0001	0.71 0.67; 1.01 0.67; 1.01 <i>p</i> =0.0001	0.61 0.54; 0.98 0.54; 0.9817 <i>p</i> =0.0001

Table 3

Bias%=Mean percentage bias (Bland Altman plot) at room temperature and at 4 °C for the samples that showed significant differences from the baseline measure (direction of bias: positive numbers represent increases over baseline, negative numbers represent decreases); 95 % CL=Lower and upper 95% confidence limits for the bias; Desirable Bias%=specification for desirable inaccuracy as published in reference 10 (see text). NA=not available.

Hours	Desirable bias% [9,10]	Room temperature (23–25 °C)				Refrigerator (4 °C)			
		8 bias% 95% CL	24 bias% 95% CL	48 bias% 95% CL	72 bias% 95% CL	8 bias% 95% CL	24 bias% 95% CL	48 bias% 95% CL	72 bias% 95% CL
parameters									
WBC (G/l)	± 6.05		–3.4 –10.3; 3.5	–7.1 –14.1; –0.2	–8.6 –14.6; –2.6				–4.4 –17; 8.1
RBC (T/l)	± 1.7	1.9 –0.2; 4.1	2.2 0.0; 4.3	2.4 0.6; 4.3	1.9 –0.0; 3.9		1.8 –0.5; 4.0	1.9 –0.1; 3.8	1.6 –0.4; 3.6
Hct (l/l)	± 1.74	3.5 1.2; 5.8	9.8 6.7; 12.8	13.2 10.2; 16.1	12.9 9.7; 16.1		2.2 0.4; 4.1	1.8 –0.4; 4.0	3.0 1.4; 4.5
MCV (fl)	± 1.26	1.67 0.55; 2.78	7.6 5.5; 9.7	10.8 8.4; 13.2	11 8.3; 13.8	0.84 –1.74; 0.06			1.3 –0.3; 2.9
MCH (pg)	± 1.35	–1.8 –3.7; 0.2	–2.0 –3.9; –0.1	–2.2 –3.9; –0.6	–1.7 –3.5; 0.0		–1.5 –3.3; 0.4	–1.7 –3.9; 0.4	–0.9 –3.4; 1.7
MCHC (g/l)	± 0.4	–3.4 –5.7; –1.1	–9.6 –12.8; –6.5	–13 –16.2; –9.9	–12.8 –16.5; –9.0		–1.8 –3.5; –0.2	–1.6 –4.1; 0.9	–2.2 –4.2; –0.2
CHCM (g/l)	n.a.	–3.3 –4.7; –2.0	–12.5 –14.6; –10.4	–17.3 –20.7; –14.0	–18.3 –21.9; –14.7	0.55 0.14; 0.96	–0.53 –1.15; 0.08	–0.88 –2.1; 0.33	–2.5 –4.6; –0.4
RDW (%)	± 1.7		1.6 –1.4; 4.6	1.6 –1.6; 4.7	1.3 –2.0; 4.5	–1.1 –2.7; 0.4		–1.5 –3.2; 0.2	–1.35 –2.8; 0.09
PLT (G/l)	± 5.9	–6.6 –15.9; 2.6	–12.1 –22.8; –1.5	–16.6 –34.4; 1.1	–19.6 –38.4; –0.8			4.1 –10.4; 18.5	1.0 –18.2; 20.3
MPV (fl)	± 2.29	18.2 12.2; 24.2	24.7 16.9; 32.5	29.2 21.5; 36.9	29.1 22.8; 35.5		13.1 3.0; 23.1	22.1 11.8; 32.3	28.3 18.7; 37.8
Reticulocyte %	± 7.8		–64.9 –105.9; –23.9	–82.5 –157.7; –7.4	–93.8 –164.8; –22.8	– –		–7.8 –26; 10.4	–14.4 –37.9; 9.1

unstable especially at room temperature and changed significantly over 24 h. Hb concentrations were stable up to 72 h at room temperature.

Each of the 12 parameters displayed a normal distribution among samples stored in the refrigerator. Statistically significant changes were found after 8 h at 4 °C in MCV, CHCM and RDW. MCV values moved up and down and were higher at 72 h. WBC, RBC, Hct, MCH, MCHC, PLT and Reticulocyte counts were stable at 4 °C for 24 h and Hb concentrations remained unchanged for 72 h. RBC, Hct, PLT, and MPV all increased over time, with maximum values at 72 h. MCH, MCHC, CHCM and Reticulocyte tended to fall with storage.

Bland-Altman analysis was performed for those parameters that differed significantly compared to the initial time points at room temperature and in the refrigerator samples. Standards for acceptable bias were originally published by Ricos et al. in 1999 [9] and the 2014 updated data has been provided on Westgard's website [10]. If the observed analytical bias is greater than the acceptable bias, results may show clinically significant differences. These comparisons are shown in Table 3, which compares the observed bias caused by storage with the desirable specification for inaccuracy [9,10].

Among the samples stored at room temperature, only WBC and RDW showed no significant difference analytically compared to desirable bias specifications over 24 h. All other parameters at 8 h showed higher bias than the specification. Among samples stored in the refrigerator for 8 h, only MCV and RDW gave lower observed bias than desirable bias.

5. Discussion

Delayed sample analysis is not at all rare in the clinical laboratory workflow because many blood samples are transported from other laboratories or health centers to the analytical laboratory. Rigorous control of pre-analytical conditions is required to maintain “good laboratory practice”. The majority of errors occur in the pre-analytical phase, including sample collection, transport and storage. Standardization of storage conditions may be critical if blood samples cannot be analyzed immediately. CBC results are affected by temperature and time since collection. Recently, Daves et al. [8] showed no changes after 3 h at different storage conditions. They found significant bias in MCH and MCV measurements after 6 h. ICSH recommended maximum storage intervals for CBC are 6 h at 18–22 °C and 24 h at 2–6 °C [6], and we set out to see if they could be extended. Our study confirmed that storage of dipotassium EDTA anti-coagulated blood samples at room temperature causes significant changes in nearly all parameters within 8 h. Our results are consistent with the ICSH recommendation [6] and differ markedly from other published studies [2,4,5]. In Table 3, column 2 we show specifications for desirable bias published by Ricos et al. [9,10]. We emphasize that most figures for observed bias in our study exceeded these values after 8 h. We were unable to obtain specifications for desirable bias for CHCM, but our data confirmed a gradual decrease in this parameter both at room temperature and at 4 °C, with different slopes.

In our opinion, similar studies to confirm the effect of sample storage should be performed in all laboratories that handle a large number of specimens collected from local and distant sources. These should result in clear published conditions for duration and temperature of sample storage before analysis in order to minimize errors.

6. Conclusion

Our studies using the ADVIA 2120 hematology analyzer indicated that blood specimens stored for up to 24 h in a refrigerator (+4 °C) may be suitable for quantitative hematological (CBC) testing. In agreement with the recommendation of the ICSH [6], the maximum storage interval for CBC parameters is less than 8 h at room temperature (23–25 °C). Only Hb concentration was stable for 72 h both at +4 °C and at room temperature.

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